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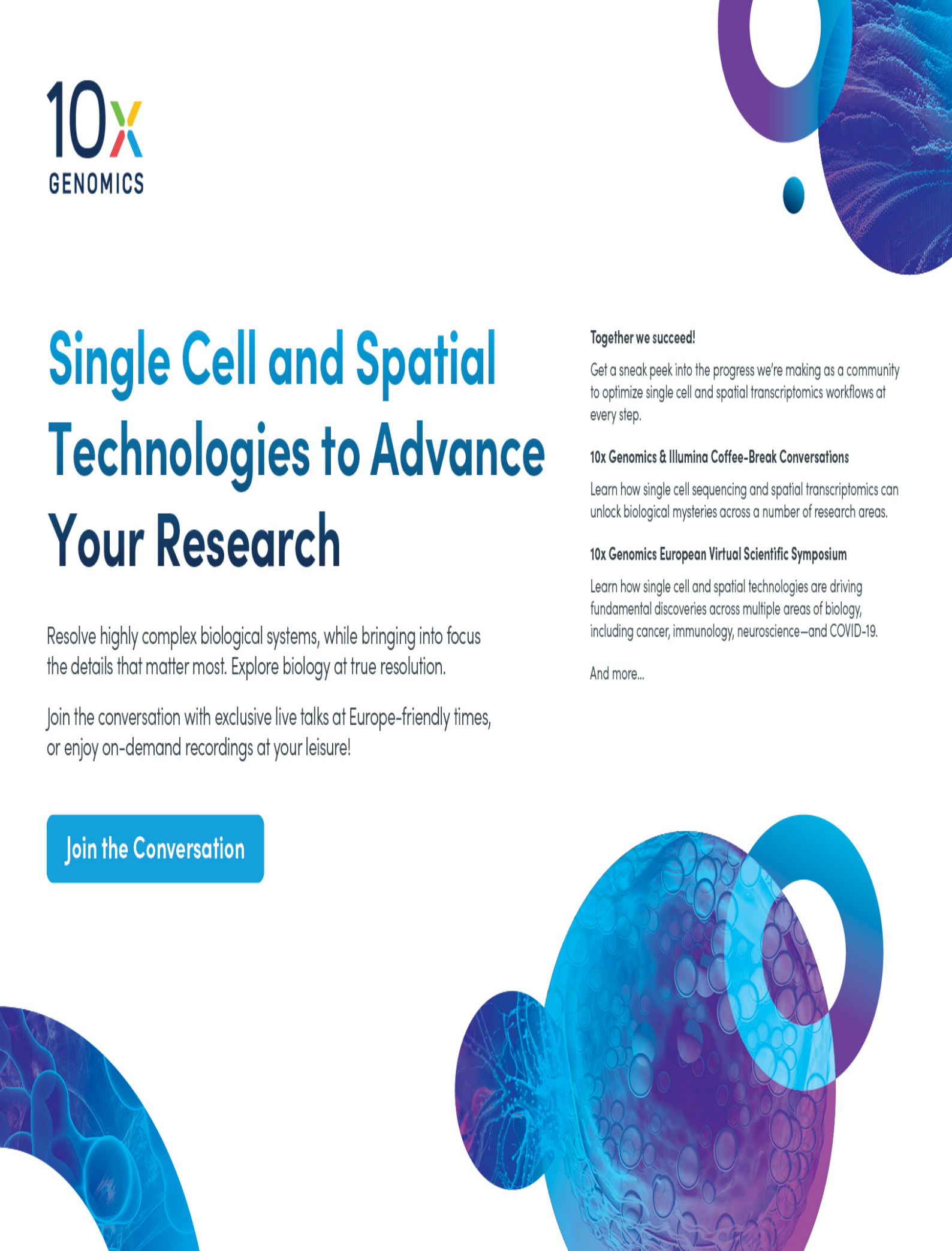

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RESEARCH REPORT

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Neural correlates of visual spatial selective attention are altered at early and late processing stages in human amblyopia

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Abstract

Amblyopia is a neurodevelopmental visual disorder which results in reduced visual acuity in one eye and impaired binocular interactions. Previous studies suggest attentional deficits in amblyopic individuals. However, spatial cues which orient attention to a visual field improved performance. Here, we investigate the neural correlates of auditory-visual spatial selective attention in amblyopia during EEG recording. An auditory cue, that was followed by the presentation of two Gabor patches presented in the lower left and right visual fields, indicated the most likely location of an upcoming target Gabor. The target Gabor differed in orientation from the more frequently presented non-target Gabor patches. Adults with amblyopia and neurotypical observers were asked to detect the target Gabor monocularly at the cued location, while withholding their response to targets presented at the uncued location and to all non-target Gabor patches. Higher response rates were observed for cued compared to uncued targets in both groups. However, amblyopic individuals detected targets less efficiently with their amblyopic eye as compared to their fellow eye. Correspondingly, event-related potentials (ERPs) recorded to the onset of the non-target Gabor patches were delayed at early processing stages (150–300 ms: posterior N100) and reduced in amplitude at later time windows (150–350 ms: P200, 300–500 ms: sustained activity) in the amblyopic eye compared to the fellow eye. Such interocular differences were not observed in neurotypical observers. These findings suggest that neural resources allocated to the early formation of visual discrimination as well as later stimulus recognition processes are altered in the amblyopic eye.

KEYWORDS

amblyopia, endogenous attention, ERPs, spatial selective attention

Abbreviations: AE, amblyopic eye; CTI, Cue target interval; EEG, electroencephalogram; ERPs, event related potentials; FE, fellow eye; ITI, intertrial interval; LE, left eye; LGN, lateral geniculate nucleus; MOT, multiple object tracking; N1, negativity after 100 ms of stimulus onset; N2, negativity after 200 ms of stimulus onset; P2, positivity after 200 ms of stimulus onset; RE, right eye; VEP, visual event- related potential.

1 | INTRODUCTION

Amblyopia (synonym: *lazy eye*) is a neurodevelopmental visual disorder which is caused by abnormal visual experience early in life (Ciuffreda et al., 1991; Levi, 2020) and results in the affected eye losing its ability to effectively drive vision. Consequently, the brain suppresses the visual information coming from the affected amblyopic eye (interocular suppression), which impairs the fusion of images needed for binocular vision (Bretas & Soriano, 2016). Losses in contrast sensitivity and visual acuity are a landmark of the amblyopic eye (Hess & Howell., 1977; Levi & Harwerth, 1977); however, amblyopic individuals show a range of sensory and oculomotor deficiencies, including higher level deficits (for recent reviews see Kiorpes & Daw, 2018, Levi, 2020; Verghese et al., 2019).

As early as 1962, Van Balen & Henkes suggested that the amblyopic eye was "inattententive", and Singer (1982) pointed to the crucial role of attention in the development of amblyopia and reported that synchronous binocular eye movements are essential for the development of normal visual pathways (Ciuffreda et al., 1979a, 1979b). Impaired eye movements, such as poor fixation stability and an increased frequency of microsaccades as observed in human observers with amblyopia have been suggested to not only impact visual perception, but also the spatial allocation of selective attention (Verghese et al., 2019).

The question of whether attentional control is impaired in human amblyopia has yielded inconclusive answers. Attentional control can be defined as the ability to focus on task-relevant information and ignore sources of distraction or noise while at the same time constantly monitoring one's environment for new sources of information (Bavelier & Green, 2019). Some studies argue that attentional control is affected in human amblyopia whereas other studies claim that individuals with amblyopia show intact attentional processes especially when attention is guided by a cue to a specific location in the visual field (see Verghese et al., 2019 for a review). Those discrepancies have also been related to differences in characteristics of the stimuli, experimental paradigms and the heterogeneity of the amblyopic population (e.g. strabismic vs. anisometropic amblyopic observers; age differences, see Tripathy & Levi, 2008).

A number of studies have used attentional cues in order to investigate the voluntary orientation of attention (also defined as top-down attentional control) in individuals with amblyopia: Sharma et al. (2000) found that amblyopic adults significantly underestimated the number of targets and missing targets when using their amblyopic eye compared to the non-amblyopic eye and neurotypical observers, which they argued as evidence for a high-level attentional deficit. Nevertheless, they also found that cueing the attention to the target location in amblyopic observers improved their performance, while cueing attention to an invalid location reduced performance. Indeed, both adults and 5–10 years old children with amblyopia benefit from the cue presentation in a similar manner to neurotypical observers by showing enhanced performance in validly cued trials compared to invalidly cued trials, and reduced performance with invalid cues (Ramesh et al., 2020; Roberts et al., 2016; Sharma et al., 2000), leading to the conclusion that covert spatial selective attention is intact in individuals with amblyopia across different age groups.

Only a few studies have investigated the neural mechanisms of spatial selective attention in individuals with amblyopia and whether brain functions in individuals with amblyopia show signatures of neural plasticity or even reorganization. The most common findings show that the amplitudes of event-related brain potentials (ERPs) recorded as a response to the visual stimuli presented to the amblyopic eye were delayed or reduced compared to the fellow eye (Arden et al., 1974; Kubova et al., 1996; McKerral et al., 1999; Sokol, 1983; Van Balen & Henkes, 1962). Hou et al. (2016) measured steady state visual evoked potentials (SSVEP) in response to flickering Gabor patches in order to understand the neural responses to fast stimulus presentation to the amblyopic or the fellow eyes in striate and extrastriate cortical areas while amblyopic individuals and neurotypical observers were cued to attend to a stimulus on the right or the left side. Amblyopic observers showed an attentional modulation when tested with their amblyopic eye corresponding to enhanced SSVEP amplitudes to the attended compared to the unattended location. This attentional modulation in SSVEP responses was, however, weaker in amblyopic observers compared to neurotypical observers. This study provides evidence for the idea that there is only a weak attentional modulation in the visual cortex of human amblyopic observers. This idea is consistent with the view that a long-term "attentional neglect" of the visual input to the amblyopic eye elicits only very small regulative effects of selective attention in the visual cortex (Hou et al., 2016).

The aim of the current study was to gain further insights into the neural mechanisms of auditory visual spatial selective attention in adult amblyopia and to link those findings to behavioural performance. We used an adapted version of the paradigm reported in Sylvester et al. (2007). Two Gabor patches (a target and a non-target) were presented simultaneously, one to the left of fixation and the other to the right, in order to avoid any automatic reorienting of attention to the stimulus onset of one Gabor patch. The target stimulus differed in spatial orientation from the more frequently presented non-target Gabor patches (see Figure 1). An auditory cue indicated the most likely location of a target Gabor patch. The observer's task was to detect this target Gabor patch at the cued location as quickly and as accurately as possible and to withhold response to target Gabor patches

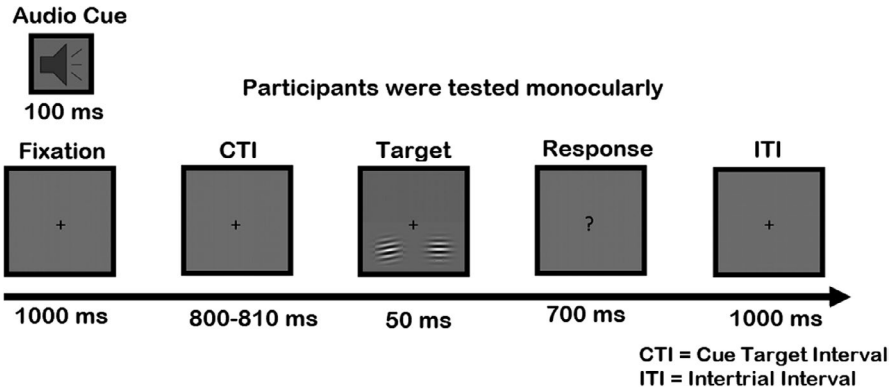

FIGURE 1 Audio-visual spatial selective attention paradigm. Participants had to maintain fixation for 1000 ms, while a 100-ms short audio cue (=left or right) was instructing the participants to guide their spatial attention to the indicated side of the screen. After a cue-to-target interval (CTI), the two Gabor patches were presented on the lower half of the screen (one left and one right). Participants had to detect the rare target Gabor patch, if any, which were rotated by 5 degrees to the left or to the right (=Target Gabor stimulus), by pressing a button during the next 700 ms, after which an intertrial interval served as a preparation phase for the following trial

at the uncued location as well as to the more frequently presented non-target Gabor patches. Trials in which the auditory cue indicated the correct location of the upcoming Gabor patch are called validly cued trials, whereas trials in which the auditory cue indicated the incorrect location of the upcoming Gabor patch are called invalidly cued trials. In most of the trials two non-target Gabor patches were presented which did not require any response. In contrast with Sylvester et al. (2007), participants were instructed to only respond to the cued targets ("Go trials") and withhold their response to all uncued (invalidly cued) targets ("No-Go trials"). This procedure allowed us to investigate whether participants were able to respond to task relevant information as well as ignore the same stimuli but at task-irrelevant spatial locations. We used a voluntary (endogenous) attention cueing paradigm, as we aimed to understand the voluntary shifts of attention to the left and right visual field without making any eye movements and whether those voluntary attention shifts differ in individuals with amblyopia and neurotypical observers. Therefore, we asked our participants to maintain central eye fixation during the trials in order reduce the number of eye movements.

In contrast with previous studies, an auditory cue was used in order to guarantee comparable guidance of attention by the cue across all participants and to avoid any possible visual masking by the cue (see also Föcker et al., 2018). To our knowledge, this is the first experimental design aimed at understanding crossmodal visual spatial attention effects monocularly by using an endogenous auditory cue followed by a bilateral visual stimulus display (see Feng et al., 2017; McDonald & Ward, 2000; McDonald et al., 2000, 2003.

Störmer et al., 2009 for exogenous auditory-visual cueing designs; and see Eimer & Schröger, 1998; Teder-Sälejärvi et al., 1999 for endogenous crossmodal attention by presenting single visual stimuli trial by trial).

We recorded electroencephalogram (EEG) signals while participants performed this task in a cross-modal Posner cueing paradigm. Our ERP analysis was grounded on the retinotopic organization of the visual system and the well-reported lateralized ERP "asymmetries of the spatial attention effects on visual ERPs" (Heinze et al., 1990; Luck et al., 1990; McDonald et al., 2005; see also McDonald et al., 2014, p. 86) similar to previous studies using visual (McDonald et al., 2014; Störmer et al., 2019) and auditory cues (Feng et al., 2017; McDonald et al., 2005, 2014; McDonald & Ward, 2000; Störmer et al., 2009, 2019). Orienting attention to one side of such bilaterally display leads to a larger ERP component and a shorter latency at contralateral occipital electrodes than ipsilateral electrodes (e.g. shorter latencies by 11 ms for N1, by 17 ms for P1; McDonald et al., 2014; by 4 ms; Luck et al., 1990; Vibell et al., 2007). These analyses were complemented by ERP analyses time locked to rare validly cued targets in the time range of the N2 component over contralateral versus ipsilateral electrode sites. The N2 is typically evoked to infrequently occurring targets which are presented among more frequently presented standards (see Folstein & van Petten, 2008; Luck, 2014; Näätänen & Picton, 1986). Furthermore, we were interested in any group differences documented by latency shifts or amplitude modulations between amblyopic and neurotypical observers as well as differences in ERPs recorded to the amblyopic eye versus fellow eye at early versus late processing stages.

Based on previous studies we hypothesized that amblyopic observers would show impaired neural processing of visual information, specifically delays in ERPs recorded as a response to the presented Gabor patches, compared to their fellow eye or to the neurotypical observers (see also Arden et al., 1974; Hou et al., 2016; Kubova et al., 1996; McKerral et al., 1999; Sokol, 1983; Van Balen & Henkes, 1962). If attentional processing differs between amblyopic and neurotypical

TABLE 1 Demographics and description in amblyopes

Participants	Age/ gender	Amblyopia type	Eye	FE vs. AE	Contrast	Refraction errors (distance)	Corrected visual acuity (logMAR)	Stereo acuity (Randot Cicles)	Treatment History
AB	27/F	Strabismus	OD	FE	0.5	20/12.5−2	−0.16	Failed	Patching
			OS	AE	0.5	20/80−1	0.62		
			OU			20/12.5−2	−0.16		
AH	44/M	Anisometropia	OD	FE	0.4	20/12.5−2	−0.16	25”	None
			OS	AE	0.4	20/40−2	0.34		
			OU			20/12.5−2	−0.16		
KS	48/F	Anisometropia	OD	FE	0.7	20/12.5	−0.20	25”	None
			OS	AE	0.7	20/40+2	0.26		
			OU			—	—		
MB	34/F	Anisometropia	OD	FE	0.5	20/12.5−1	−0.18	70”	Patching
			OS	AE	0.5	20/50	0. 40		
			OU			20/12.5	−0.20		
AS	28/F	Anisometropia	OD	FE	0.5	20/16−2	−0.06	70”	Vision Training
			OS	AE	0.5	20/40+1	0.28		
			OU			20/16−1	−0.08		
MV	41/F	mixed	OD	FE	0.5	20/20−2	0.04	70”	-
			OS	AE	0.5	20/40−1	0.32		
			OU			20/16−2	−0.06		
EM	64/F	Aniso-metropia	OD	FE	0.5	20/16	−0.10	Failed	Patching
			OS	AE	0.5	20/60−1	0.5		
			OU			—	—		

Abbreviations: “—”, Missing data; AE, amblyopic eye; FE, fellow eye; OD, oculus dexter = right eye; OS, oculus sinister = left eye; OU, oculus uterque = both eyes.

observers, we would expect differences in performance between both groups to validly cued targets compared to invalidly cued targets. Those performance differences would be accompanied by distinct modulations of standard and target ERPs recorded to the cued Gabor patches over contralateral versus ipsilateral electrodes in amblyopic observers compared to neurotypical observers.

2 | METHOD

2.1 | Participants

Thirteen amblyopic and 10 neurotypical observers participated in the experiment. One control participant and one participant with amblyopia had exceptionally low behavioural performance (less than 30% hit rates) and were, thus, excluded from the final sample. From the remaining participants, seven individuals with amblyopia and seven neurotypical observers had EEG data of sufficient quality and provided enough EEG artefact free experimental trials for further analyses. Therefore, the reported findings are based on the final sample of these 14 participants. The behavioural data in the excluded participants were screened and were found to be similar to those of the subjects in the final sample. The final sample consists of seven neurotypical observers (age range: 22–38 years, mean 28.66 years, *SD*: 7.033, one missing age information; one male, six females, five indicated a left dominant eye), and seven individuals with amblyopia (age range: 27–64 years, mean: 39.85 years, *SD*: 12.53; one male, six females, left amblyopic eye in all subjects). Age did not significantly differ between the two groups (t (11) = 1.934, p = .079). The sample size, although small, is similar to that of several previous EEG studies in individuals with impaired vision such as developmental cataracts (e.g. Bottari et al., 2016; Röder et al., 2013) . Patients were recruited through the clinical coordinator at the School of Optometry Clinic at UC Berkeley, and through the Smith Kettlewell Eye Institute in San Francisco, CA. Neurotypical control subjects were recruited at the University of California, Berkeley.

Before the start of the actual experiment, all participants underwent an initial screening in the lab that included: LogMAR visual acuity (VA), isolated VA, near VA, ophthalmoscopy, stereo-acuity tests (Randot circles and preschool stereotests), fixation- and worth 4-dot-tests. To meet the inclusion criteria for the study, participants with amblyopia had to manifest: acuity in the amblyopic eye between 20/30-20/400, a minimum of two line interocular difference in acuity with best correction, no ocular pathology or nystagmus, and 20/20 or better in the fixing (non-amblyopic) eye.

To be categorized as an anisometrope, patients had to have at least one diopter difference between the two eyes. Patients with an eye-turn were classified as strabismic, and those with both anisometropia and strabismus were classified as mixed. Most of the individuals with amblyopia (5/7) had anisometropia. Clinical details of the amblyopia sample are listed in Table 1.

TABLE 2 Demographics and description in neurotypical observers

Participants	Age/ gender	Eye	Eye dominance	Contrast
AR	24/F	OD	—	0.4
		OS	—	0.4
GM	37/F	OD	NE	0.4
		OS	DE	0.4
GW	24/F	OD	NE	0.4
		OS	DE	0.4
JL	22/F	OD	DE	0.4
		OS	NE	0.4
MN	38/F	OD	NE	0.4
		OS	DE	0.4
NV	—/F	OD	—	0.4
		OS	—	0.4
TJ	27/M	OD	NE	0.4
		OS	DE	0.4

Abbreviations: "—", Missing information; DE, dominant eye; NE, non-dominant eye; OD, oculus dexter = right eye; OS, oculus sinister = left eye.

Inclusion criteria for neurotypical controls were: normal or corrected-to-normal visual acuity in both eyes (20/20 or better), no optical pathology and no previous treatment for amblyopia. A more detailed description of the controls' characteristics is presented in Table 2.

Participants that met inclusion criteria in assessment 1 returned to the lab for a second assessment visit, in which their visual acuities and suppression were tested with greater precision using Matlab programs (measure letter acuity, grating acuity, stereo-acuity and suppression). In order to control for low-level losses of contrast sensitivity, amblyopic observers completed blocks of the Posner cueing paradigm with either their amblyopic eye or their fellow eye, while a staircase procedure was used to determine the contrast level resulting in ≈ 80% correct performance, similar to performance of the neurotypical observers at a contrast level of 40%. Findings in Section 4.1.5 indicate that this contrast level adaption for the amblyopic observers was successful. For neurotypical controls, the same contrast values were used for all participants eyes (left eye and right eyes), namely a value of 0.4 for both eyes. Based on previous literature, a contrast of 40% was chosen for the neurotypical participants to maintain a good electrophysiological signal (signal to noise ratio) and at the same time require participant's attention (see also Levi & Harwerth, 1978. Forty percent is well above threshold, moreover, the Visual Event-related potential (VEP) signal typically saturates at contrast levels above 40% (see also Levi & Harwerth, 1978).

Eye dominance was measured in the neurotypical observers using a hole in the card test and did not play a role in our analyses, since the study's main concern was the interocular dynamics in amblyopic patients. Following the initial assessments, participants then completed the cross-modal attention task. All participants reported having normal hearing.

2.2 | Stimuli and apparatus

The experiment took place in a sound-attenuated room (EEG Laboratory) in moderate brightness indoor lighting conditions. Participants sat at a table in front of a 17 inch Sony Trinitron CRT monitor with a refresh rate of 100 Hz and a display resolution of 1,024 × 768 pixels. The viewing distance was 50 cm for all participants. A chin and forehead rest, which was fixed to the table, was used throughout the experiment to aid in head stabilization.

Gabor patches served as the visual stimuli and were either horizontally oriented (=Standard Gabor patches) or tilted clockwise or counter-clockwise by 5 degrees (=Target Gabor patches). The visual stimuli were presented on a gray background with an approximate luminance of 13 cd/m^2. Participants were informed that eye movements were visible in the recorded EEG and were therefore asked to avoid making eye movements during an experimental trial. We used a spatial frequency of 3.5 cycles per degree, based on previous work showing that spatial frequencies around 2 to 4 c/deg result in maximum signal to noise ratios in amblyopic observers viewing with their amblyopic eye (see Levi & Harwerth, 1977). Two loudspeakers were positioned to the left and right side of the computer screen. Auditory stimuli (=cue) consisted of the recorded words *Left* or *Right* presented for 100 ms. The audio cues were presented from two loudspeakers at an individually adjusted sound volume (dB was adjusted during the practice block if participants had difficulties hearing the cue properly and that remained unchanged after starting the first experimental block).

2.3 | Procedure

As Figure 1 illustrates, a trial started with the presentation of an auditory cue (a female voice saying *left* or *right*, duration: 100 ms) presented via two loudspeakers which instructed participants to direct their spatial attention to either the left or right lower half of the screen, while fixating on a fixation cross presented at the centre of the screen. After a cue-target-interval (CTI) of 800 ms (with a varying jitter of maximum 10 ms), two Gabor patches were briefly presented on the screen (50 ms), at a 5° diagonal in the lower left and right peripheral quadrants. On 80% of the trials, the stimuli were two horizontally oriented standard non-target Gabor patches (standard trials). On 20% of the trials, a standard Gabor patch appeared in one of the two locations, and a target Gabor patch was presented in the other location (target trials). The target patch differed in orientation from the more frequently presented non-target Gabor patches. Participants were instructed to respond as quickly and accurately as possible by pressing a specific button with their right index finger when they detect the rotated target Gabor patch at the cued location (validly cued target trials). On half of the trials including a target stimulus, the target appeared at the un-cued location (invalidly cued target trials). Participants were instructed to respond only when target stimuli were presented in the cued location and were told to withhold response in the standard and invalidly cued target trials. Thus, in trials that included two standard Gabor patches (80% of the trials), no response was required. An intertrial interval (ITI) of 1,000 ms was presented subsequently after the response-time.

All participants were tested on this Posner cueing task, while EEGs were recorded. Each participant performed the experiment twice and each time monocularly. Therefore, each participant was tested one time with the right eye only (left eye was patched) and one time with the left eye only (right eye was patched). The order of the experiment (start with the left or right eye) was counterbalanced across participants.

2.4 | Design

Each experimental run started with one or more (if needed) blocks of practice trials. Following practice, most participants completed, on average, 10 blocks (5 blocks with each eye)—but tried to finish as many blocks and trials as possible during the testing time, which varied depending on the time needed for placing the EEG cap and electrodes on the subject's scalp—resulting in a total of about 400 trials for each eye (320 standard trials, 80 target trials). Trial types were randomized within each block throughout the experiment.

2.5 | EEG data acquisition and analyses

Scalp potentials were recorded from 66 electrodes using a BioSemi system (BioSemi) and the electrode labels approximated those of the 10–20 system. Scalp and mastoid electrode impedances were maintained below 10Ω. Scalp potentials were referenced to the Cz channel during recording. The recorded scalp activity was amplified with a band pass of 0.1–80 Hz. Signals were digitized at a sampling rate of 200 Hz with a gain of 10,000.

EEG data were analysed in Matlab (Mathworks, Inc.) using EEG-Lab/ERPLab toolbox (Delorme & Makeig, 2004; Lopez-Calderon & Luck, 2014). The data were first digitally re-referenced to linked mastoids and then bandpass filtered

offline with a half amplitude cut-off of 0.1–40Hz (non-causal Butterworth impulse response function, −6 dB/octave).

A short epoch consisting of a 500 ms activity starting from the onset of the standard Gabor patches (non-target Gabor patches) was formed in order to study ERP components that appear earlier in time and tend to have shorted latency ranges. Another longer epoch of 800 ms starting from the onset of the standard Gabor patches (non-target Gabor patches) was created to investigate later ERP activities that tend to have longer latency ranges. The earlier and later ERP components were studied using epochs of two difference lengths. This is because, generally, earlier ERP components, as compared to the later ones, need a higher signal to noise ratio in order to be precisely quantified. Short epochs tend to survive the artefact rejection procedure more than the longer epochs and, thus, preserve a high signal to noise ratio in order to look at the early components. The longer epoch will have a sufficiently high signal to noise ratio to study the later ERP components such as sustained activities that come later in time. The shorter and longer epochs during which a motor response took place (i.e., false alarms) were excluded from further ERP analyses. Beside these epochs which were time-locked to the onset of standard (non-target) Gabor patches, a short epoch of 500 ms was created that was time-locked to the onset of validly cued target Gabor patches which were correctly detected and responded to (i.e., Hit trials for validly cued targets). All epochs included a 200 ms baseline activity and were all baseline corrected using the mean voltage over 200 ms pre-event period (the Cue-Target Interval period). No systematic changes in the baseline activity were observed between different groups and experimental conditions.

Noisy channels were detected visually using the channel data scroll and were manually interpolated (replaced by the average of the six nearest spatial neighbour electrodes). Any epoch with EEG artefacts, defined as any voltage exceeding ± 75μv or a difference between two consecutive data points exceeding 50μv, were excluded from further analysis. Epochs with ocular artefacts were removed by applying the step-like artefact rejection function (window size: 400 ms, step-size: 50 ms, threshold: 20μv) of ERPLab toolbox (Delorme & Makeig, 2004) to the activity of the two fronto-polar channels (FP1 and F1). The rejection voltage thresholds had to be adjusted for many participants of both experimental groups. Despite this adjustment, careful visual inspection of epochs after artefact rejection ensured the absence of artefacts for these participants. The epochs were then averaged for each participant and for each eye and experimental condition. These average activities were used to quantify and study the ERP components of interest.

Visual inspection of a collapsed-localizer (Luck & Gaspelin, 2017) as well as the grand average (GA) waveforms and topographies of the individual experimental conditions determined the ERP components to be studied and the appropriate time-windows to investigate different attributes of these components (i.e., amplitude and latency). In the short (500 ms long) epoch time-locked to the onset of the standard Gabor patches: (a) an early negativity at the posterior sites similar to the posterior N1 reported in the past literature was observed and its peak amplitude and peak latency were calculated in the latency range of 150–300 ms post-onset of the standard Gabor. (b) an anterior P2 component, shown as a positive peak in the central-anterior sites, was investigated using its peak amplitude and peak latency in the time range of 150–350 ms post-onset of the standard Gabor patches. In the longer epoch (800 ms long) time-locked to the onset of the standard Gabor patches: a late positive sustained activity following the onset of the standard Gabor patches (300–700 ms) was studied using a mean amplitude measure in their respective latency ranges. This period of 400 ms was divided into two smaller 200 ms time-windows, named the earlier (300–500 ms) and later (500–700 ms) complexes, in order to better capture the temporal progression of neural activity in later stages of processing. As for the epochs time-locked to the onset of validly cued targets, which were correctly detected and reported, we investigated a posterior N2 component, shown as a negative peak in lateral-posterior sites (resembling the topography of the well-documented N2PC component), using its peak latency in the time-rage of 150–300 ms post-onset of a target Gabor. All peak amplitude and latency measures were determined for a component using a local peak, defined as the most positive/negative point which was higher than 5 points preceding it and 5 points following it in that specific time-window used to study the component. If no points fulfilling these criteria were found, an absolute peak was used instead, defined as the most positive/negative point in the given time-window. The process of finding and quantifying peak/mean amplitude and latency measures was performed automatically using computerized algorithms of the ERPLab toolbox (Delorme & Makeig, 2004).

The choice of the electrode clusters to be studied for each component was guided by regions of more prominent activity in the grand-average waveforms and the topography maps. These sites had to be consistent with the ones used in past research to study the component in question. In order to avoid a selection bias, collapsed localizers, averaging the ERPs over all experimental conditions and both groups, were consulted and contributed significantly to the choice of electrode sites and clusters that were more closely investigated (Luck & Gaspelin, 2017).

3 | ANALYSIS

3.1 | Analysis of behavioural data

The response rate for validly cued target trials was calculated as the number of correctly identified target Gabor patches

at the cued location divided by the total number of target Gabor patches presented at the cued location separately for each eye (amblyopic eye vs. fellow eye or left vs. right eye). The response rate for invalidly cued trials was defined as the number of responses to target Gabor patches at the uncued location divided by the total number of target Gabor patches presented at the uncued location separately for each eye (amblyopic eye vs. fellow eye or left vs. right eye). The miss rate was calculated as 1- response rate separately for cued and uncued trials and the eye being tested.

We used a mixed, repeated measures analysis of variance (ANOVA) to analyse the dependent variables (response rate and misses), with the between-subject factor *Group* (NTO = Neurotypical Observers vs. PA = Participants with amblyopia), and the two within-subject factors *Eye* (LE = left eye in NTOs/ AE = amblyopic eye in PAs vs. RE = right eye in NTOs/ FE = fellow eye in PAs), and Cue (validly cued vs. invalidly Gabor patches).

In line with the task instructions to withhold responses to invalidly cued Gabor patches, we observed a very low response rate in the invalidly cued target trials (see Section 4.1). Thus, only the validly cued responses to target trials (hits) were used to further analyse the other three dependent variables D-prime, reaction times (RTs), and inverse efficiency scores (IE scores). Thus, the factor Cue was not included in the ANOVA analyses of these behavioural measures. D-prime served as a sensitivity index and was computed with the following formula: z(Hit rate)—z(FA-rate) that was adjusted with the log-linear approach in order to correct for the z-transformed Hit and FA proportions ($p = 0$ or $p = 1$) that take on infinite values (Hautus, 1995). Thus, the log-linear rule was applied by adding 0.5 to both: the number of Hits and the number of FAs, and adding 1 to both: the number of signal trials and the number of noise trials. Reaction times were calculated as the time between the onset of the target Gabor and the execution of a manual response. Inverse efficiency scores were calculated for each participant by dividing the mean response times by the proportion of correct trials (responses to targets and no-responses to non-targets, Townsend & Ashby, 1978). Similar to RTs, lower IE values indicate better performance. Follow-up post hoc analyses were performed on any significant ($p < .05$) main effects and interactions to investigate the effects' characteristics in detail.

3.2 | Analysis of ERP data

To examine amplitude and latency characteristics of the ERP components, each ERP measure of each component was submitted to a mixed, repeated measures ANOVA with the between-subject factor *Group* (NTO = Neurotypical Observers vs. PA = Participants with amblyopia), and the two within-subject factors *Eye* (LE/AE vs. RE/FE; Left Eye/Amblyopic Eye vs Right Eye/Fellow Eye), *Laterality* with respect to the cued spatial location of the visual field (Contra = contralateral vs. Ipsi = ipsilateral to the attended stimulus location). According to the method explained in Section 2.5, appropriate electrode sites were selected for each component and the above described statistical analyses were run on the ERP measures quantified from these sites. For each ERP component, the activity of electrode sites which were in the spatial vicinity of one another and would usually show similar trends in the collapsed-localizer waveforms and topographies were grouped together, forming electrode clusters of 3–5 electrode pairs. For each component, the activity of electrode sites showing similar trends were grouped together, forming electrode clusters of 3–5 electrode pairs. This captures more accurately the spread of the ERP activities observed in the scalp maps, increases the signal to noise ratio, lowers the risk of statistical type 1 error, and better represents the low spatial resolution of ERP components (Luck & Gaspelin, 2017). Amplitude or latency of any investigated ERP component was calculated accordingly for each eye of each subject, using the ERP activity of the selected electrode cluster for that component, and was then used in statistical analyses.

Any main and interaction effects (under a significance level of $p < .05$) were investigated further using appropriate follow-up post hoc tests run separately on different groups or experimental conditions. All statistical analyses were performed using the Microsoft Excel program and the IBM SPSS Statistics software package. Descriptive statistics are reported as the mean and corresponding standard deviation/ standard error. The significance level was set at $p < .05$. If sphericity was violated, statistical values had been adjusted with the Greenhouse Geisser correction. Through artefact rejection steps, some trials were accepted as artefact-free and some were declared as artefactual. Only the artefact-free trials, which include high signal to noise ratio, were used for further ERP analyses. Statistical analyses were performed comparing the number of trials between experimental groups and conditions. This was done in order to ensure that possible significant differences between groups or experimental conditions (regarding the amplitude or latency of ERP components) are not due to different number of artefact-free trials used to quantify the measures of the ERP components. The comparisons showed that the number of artefact free trials did not differ between the amblyopic ($M = 376$, $SE = 15$) and the neurotypical observers ($M = 393$, $SE = 15$) and also no difference was found between the left/amblyopic, since all of the amblyopic eyes were left eyes ($M = 397$, $SE = 17$) and right/fellow ($M = 355$, $SE = 26$) eyes of the participants (main effect of Eye: $F(1,12) = 0.604$, $p = .452$, main effect of Group: $F(1,12) = 0.653$, $p = .453$, interaction Eye*Group: $F(1,12) = 1.170$, $p = .301$). The analyses described above were also performed on the number of ocular artefacts (e.g., blinks and saccades) specifically, as this kind of artefact has the potential to influence results coming from any experimental paradigm entailing visual stimuli. The ocular artefacts were found to be comparable between the amblyopic

observers and neurotypical observers, a pattern which was also found between the left/amblyopic eye and right/fellow eye (main effect of *Group*: $F(1,12) = 2.355$, $p = .151$; main effect of Eye: $F(1,12) = 0.144$, $p = .711$, interaction Eye * Group: $F(1,12) = 0.466$, $p = .508$). Thus, the signal to noise ratio in general and ocular artefacts specifically are comparable between our groups and experimental conditions. Therefore, ERP and behavioural measurements, do not seem to be erroneously influenced by these factors.

The Spearman correlation was used to investigate the relationship between the significant attention-related shifts of amplitude or latency in any of the ERP components to standard trials (defined as attenuated/delayed ERP peaks over ipsilateral electrode sites vs. contralateral electrode sites) and the contrast values measured when testing the amblyopic eye. This was performed in order to investigate whether reduced contrast sensitivity in the amblyopic eye is related to any possible attentional modulations. Post hoc analysis showed a main effect of *Latency* in the posterior N1 to standard trials. Therefore, the analysis was focused on this component.

4 | RESULTS

4.1 | Behavioural results

4.1.1 | Cueing effects

Response rate to target Gabor patches

The response rates for both amblyopic and neurotypical observers are shown in Figure 2a,b. The ANOVA including the between-subject factor *Group* (Neurotypical vs. Amblyopic observers) and the within-subject factors *Eye* (LE/AE vs. RE/FE) and *Cue* (validly cued compared to invalidly cued) on the response rates revealed a significant main effect of *Cue* ($F(1,12) = 350.508$, $p < .001$, $\eta_p^2 = 0.967$) with a higher number of responses in validly cued trials (mean = 0.794, $SE = 0.041$) compared to invalidly cued trials (mean = 0.016, $SE = 0.005$). The three way interaction between the factors *Cue*Eye*Group* was also significant ($F(1,12) = 13.160$, $p = .003$, $\eta_p^2 = 0.523$). Both neurotypical observers and individuals with amblyopia had higher response rates to validly cued Gabor patches compared to invalidly cued Gabor patches in both eyes. However, for neurotypical observers, the response rate in the validly cued trials was lower in the right eye compared to the left eye (as revealed by paired-samples *t*-tests contrasting cued trials right eye vs. left eye: $t(6) = 3.573$, $p = .012$, uncued trials right eye vs. left eye: $t(6) = 1$, $p = .356$). There was no interocular difference in response rates in the validly cued or invalidly cued trials between the amblyopic and the fellow eyes of individuals with amblyopia (paired-samples *t*-tests contrasting cued trials amblyopic eye vs. fellow eye: $t(6) = -1.828$, $p = .117$, un-cued trials left vs. right eye: $t(6) = 0.800$, $p = .454$). The main effect of *Group* was not significant (main effect of *Group*: $F(1,12) = 0.336$, $p = .573$, see Figure 2a,b), rendering the groups similar in response rates.

Misses

The ANOVA on the miss rate to target Gabor patches also showed a significant main effect of *Cue* ($F(1, 12) = 350.508$, $p < .001$, $\eta_p^2 = 0.967$), revealing a higher number of misses on

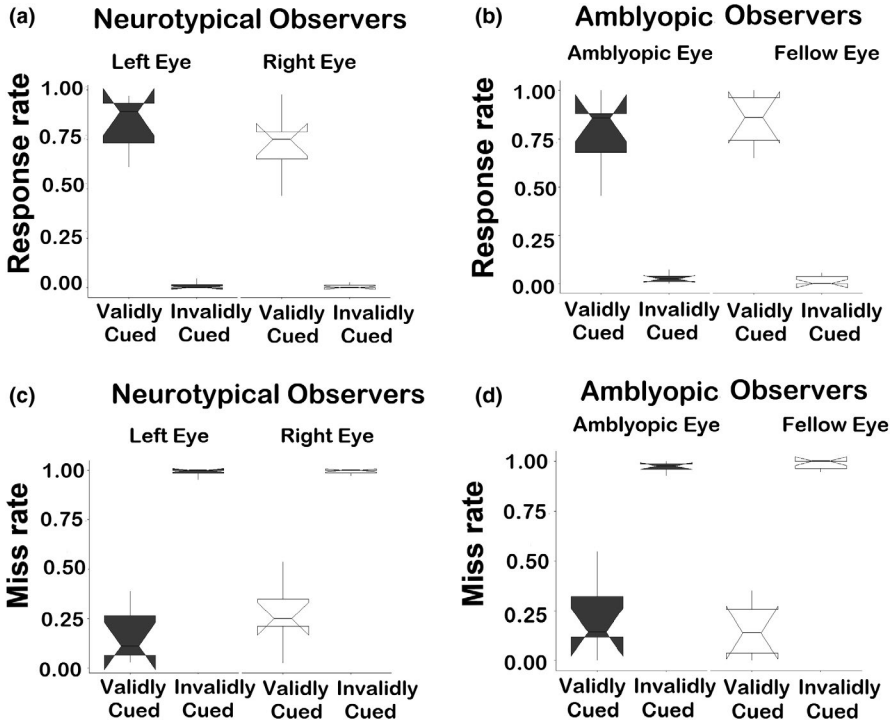

FIGURE 2 Box-whisker plots showing the response rate (a, b) and misses (c, d) separately for the amblyopic and fellow eyes of the amblyopes (amblyopic eye: grey, fellow eye: white) and separately for the right and left eyes of the neurotypical observers (left eye: grey, right eye: white). Box and whiskers show the spread of the measures (minimum, first and third interquartile ranges, and maximum. The notch in the boxplots indicates 95% confidence intervals. Stars indicate$p < .05$

invalidly cued trials (mean = 0.984 , SE = 0.003) compared to validly cued trials (mean = 0.206, SE = 0.041). The interaction between *Cue*Eye*Group* was significant ($F(1,19) = 13.160$, $p = .003$; $\eta_p^2 = 0.523$). Neurotypical observers showed higher miss rates in the validly cued right eye compared to the validly cued left eye ($t(6) = -3.573$, $p = .012$; uncued right vs. left eyes: $t(6) = -1.000$, $p = .356$). However, this interocular difference was not observed in amblyopic observers (cued right eye vs. left eye: $t(6) = 1.828$, $p = .117$; uncued right eye vs. left eye: $t(6) = -0.800$, $p = .454$). The main effect of *Group* was not significant $F(1,12) = 0.146$, $p = .709$, see Figure 2 C,D), showing comparable miss rates in the two groups.

Due to the very low response rate in the invalidly cued target trials (see Section 4.1) which suggest that participants were following task instructions, we only investigated the validly cued target trials on the other three dependent variables D-prime, reaction times (RTs) and inverse efficiency scores (IE scores).

4.1.2 | D-prime

The ANOVA including the between-subject factor *Group* (Neurotypical Observers vs. Amblyopic observers) and the within-subject factor *Eye* (LE/AE vs. RE/FE) on D-prime revealed a significant interaction between *Eye* and *Group* ($F(1, 12) = 5.597$, $p = .036$, $\eta_p^2 = 0.318$). The follow-up post hoc test revealed no interocular differences between the amblyopic eye (mean = 3.44 d', $SE = 0.275$) and the fellow eye (mean = 3.64 d', $SE = 0297$) within amblyopic observers. However, the difference between the left (mean = 3.987 d', $SE = 0.275$) and the right eyes (mean = 3.479 d', $SE = 0.297$) of the neurotypical observers was significant (p = .027). No other main effects of *Eye* or *Group* reached statistical significance ($p > .05$).

4.1.3 | Reaction times

The ANOVA on RTs showed a significant main effect of *Eye* ($F(1, 12) = 11.195$, $p = .006$, $\eta_p^2 = .483$), revealing longer RTs for the LE/AE (mean = 623 ms, $SE = 13$) compared to the RE/FE (mean = 608 ms, $SE = 14$). The main effect of *Group* and the interaction between *Eye* and *Group* were not significant (*Group*: $F(1,12) = 3.127$, $p = .102$; interaction between *Eye* and *Group*: $F(1,12) = 2.929$, $p = .113$).

4.1.4 | Inverse efficiency scores

The ANOVA on inverse efficiency (IE) values showed a significant main effect of *Eye* ($F(1, 12)= 5.939$, $p = .031$, $\eta_p^2 = 0.331$) revealing less efficient performance (i.e., higher I.E scores) when testing the LE/AE (mean = 639.7, $SE = 16.12$) compared to the RE/FE (mean = 626.688 ms, $SE = 17.224$) (see Figure 3). Moreover, a significant interaction between *Eye* and *Group* ($F(1, 12) = 6.524$, $p = .025$, $\eta_p^2 = 0.352$) was found, suggesting the amblyopic eye (mean = 624.6 ms, $SE = 26$) being less efficient compared to the fellow eye (mean = 597.7 ms, $SE = 28.18$) within the amblyopic observers ($t(6) = 2.959$, $p = .025$). By contrast, no such significant differences between the left (mean = 654.96 ms, SE = 18.9) and the right eye (mean = 655.59 ms, $SE = 19.8$) was observed in neurotypical observers ($t(6) = -0.109$, $p = .917$). The main effect of *Group* was not significant ($F(1,12) = 1.793$, $p = .205$, see Figure 3).

4.1.5 | Correlations between D-prime with reaction times

There was a significant negative correlation between D-prime and RTs for the amblyopic eye and the fellow eye (amblyopic eye: $r(7) = -.904$, $p = .005$; fellow eye: $r(7) = -.806$, $p = .029$) suggesting that the contrast adaptation procedure run for the amblyopic observers was successful (Figure 4). The correlation between D-prime and RTs for neurotypical observers was significant for the left eye ($r(7) = -.826$, $p = .022$) but not for the right eye ($r(7) = -.454$, $p = .306$).

4.2 | Visual ERPs

In the following section, the results of the analyses on the peak and latency attributes of the ERP components time-locked

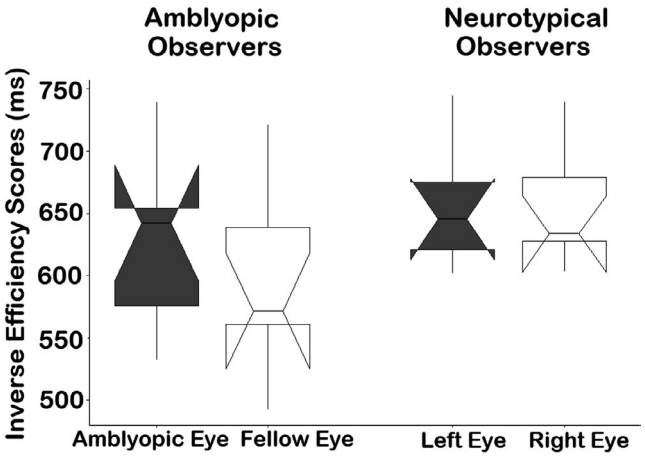

FIGURE 3 Box-whisker plots showing inverse efficiency scores (ms) separately for the amblyopic and fellow eyes of the amblyopes (amblyopic eye: grey, fellow eye: white) as well as for the left and right eyes of the neurotypical observers (left eye: grey, right eye: white). Box and whiskers show the spread of the measures (minimum, first and third interquartile ranges, and maximum. The notch in the boxplots indicates 95% confidence intervals. Stars indicate$p < .05$

to the onset of the standard Gabor patches are presented. Figures 5 and 6 show the grand-average waveforms and the corresponding scalp maps of the ERP activities in the time-range of the posterior N1, P2, and late sustained positive complexes. Figure 5 shows the N1 at a posterior electrode cluster separately for the both eyes in the amblyopic observers as well as the neurotypical observers. Moreover, Figure 5 illustrates also the ERPs in the time range of P2 at a fronto-central electrode cluster separately for both eyes in the amblyopic observers and neurotypical observers. Figure 6 represents the ERPs contralateral versus ipsilateral to the cued standard Gabor patches (A) and target Gabor patches (B). Figure 7 represents the later sustained positive activity at a central-posterior electrode cluster for both eyes in the two groups. Figure 8 represent box-whisker plots of all ERP components.

4.2.1 | Posterior N1 (150–300 ms)

The posterior N1 component was studied using the most negative local peak in the time-window of 150–300 ms post-onset of the standard Gabor patches. The latency of this peak was considered the peak latency of the posterior N1 component. The findings are presented for a posterior cluster including electrode pairs P5/P6, PO3/PO4, PO7/PO8 and O1/O2.

4.2.2 | Posterior N1: Peak amplitude

For the peak amplitude of the posterior N1 component, none of the main or interaction effects of the ANOVA analyses were statistically significant (all p-values >0.1), rendering the groups, eyes and activity sides comparable to each other.

4.2.3 | Posterior N1: Peak latency

The ANOVA analyses on the peak latency of the posterior N1 component revealed a significant interaction between the factors *Eye* and *Group* ($F(1,12) = 8.144$, $p = .015$, $\eta_p^2 = 0.404$). Post hoc analyses showed that the N1 peak latency was comparable between the right and left eyes of the neurotypical observers ($t(6) = -0.855$, $p = .425$; left eye: mean = 199.416 ms, SE = 5.580; right eye: mean = 200.426 ms, SE = 5.794). However, the N1 peak latency was significantly delayed in the amblyopic eye compared to the fellow eye of the amblyopic observers ($t(6) = 2.723$, $p = .035$; amblyopic eye: mean = 226.99 ms, SE = 5.580; fellow eye: mean = 215.395 ms, SE = 5.794). Moreover, the ANOVA revealed a significant main effect of *Group* ($F(1,12) = 7.136$, $p = .020$, $\eta_p^2 = 0.374$), suggesting a delayed posterior N1 for individuals with amblyopia as compared to the neurotypical observers (amblyopia: mean = 220.762 ms, SE = 5.499, neurotypical observers: mean = 199.921, SE = 5.499; amblyopic observers: $t(6) = 2.723$, $p = .035$; see Figure 5). Additionally, the main effect of *Eye* was significant. Latencies were longer for the left/amblyopic eye (mean = 212.722 ms, SE = 3.946) compared to the right/fellow eye in the entire sample (mean = 207.91 ms, SE = 4.097, see Figure 8a). Since the right and left eyes of the neurotypical observers had comparable peak latencies, it could be assumed that the observed significant main effect of eye is driven by the strong inter-ocular

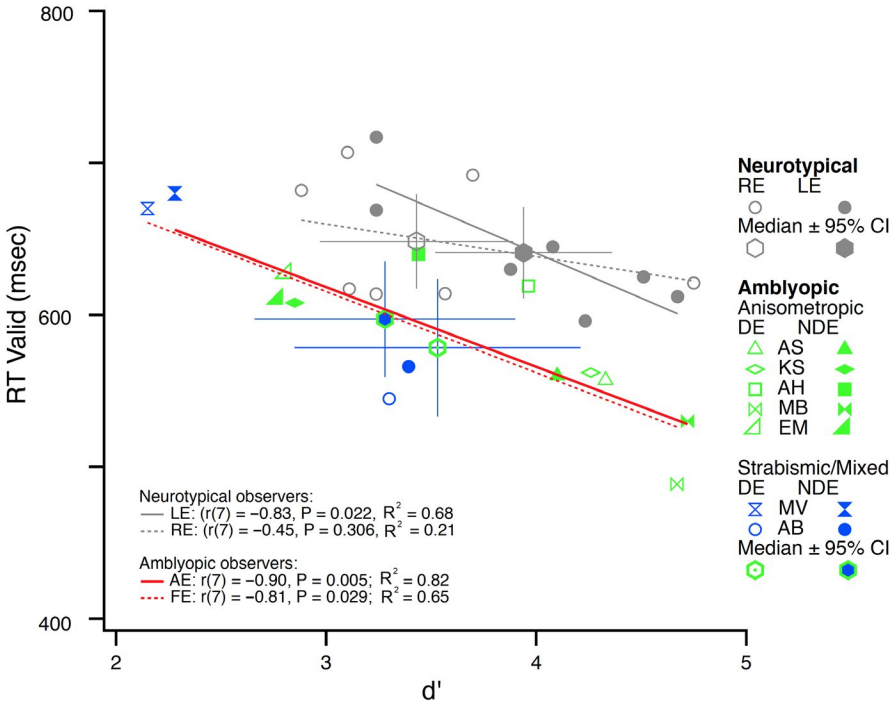

FIGURE 4 Correlations between reaction times (RTs) and d-prime in neurotypical observers (grey dashed line: right eye, grey solid line: left eye) and in amblyopes, separately for the amblyopic eye (red dashed line) and the fellow eye, (red solid line)

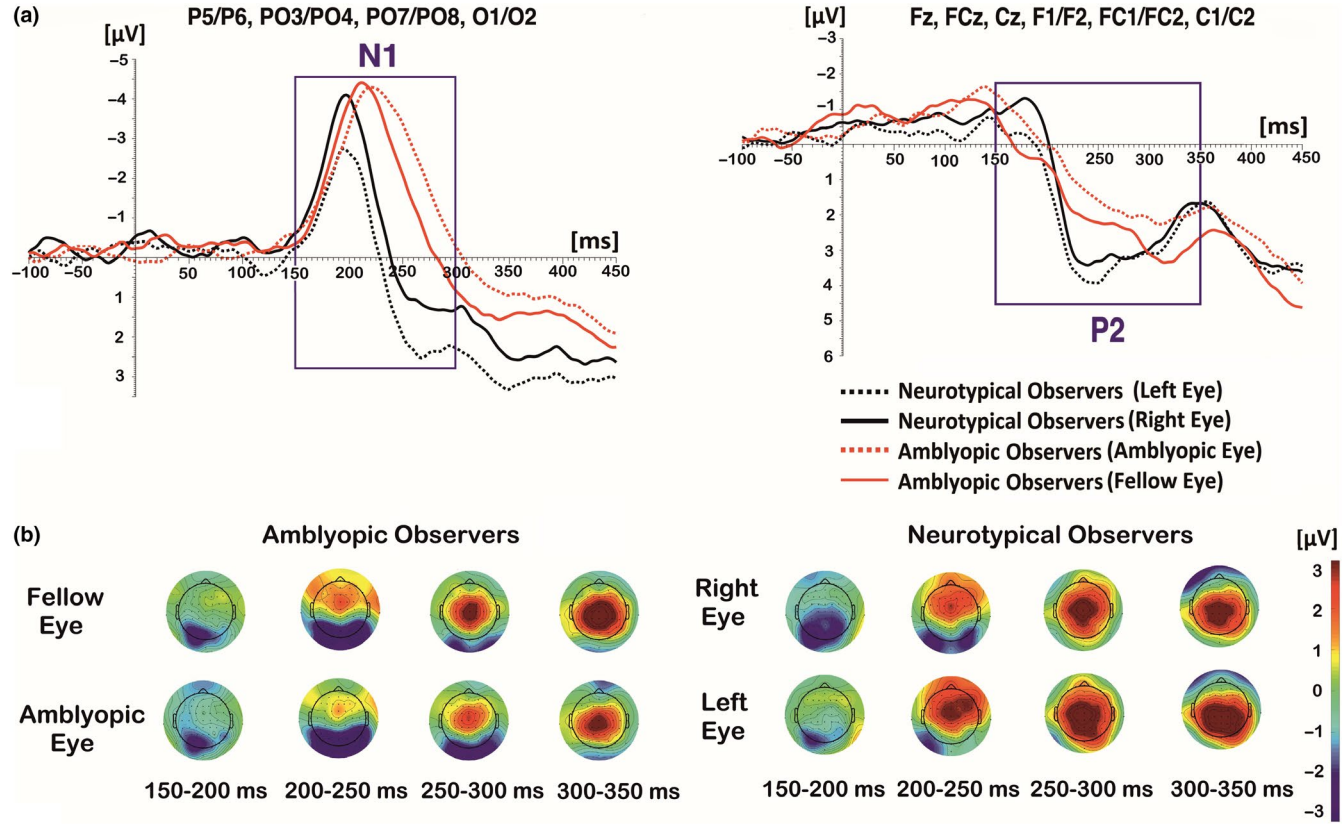

FIGURE 5 Left side—Posterior N1 ERP component (150–300 ms): (a) Grand-average waveforms of the ERPs recorded to the standard Gabors (including only non-target Gabor patches) when testing the amblyopic eye (red dashed line) and the fellow eye (red solid line) in amblyopes, and the left (black dashed line) and right eye (black solid line) in neurotypical observers. (b) Topographical scalp maps of the ERP activity. Waveforms and scalp maps indicate a delayed posterior N1 peak for the amblyopic eye. Right side—P2 ERP component (150–350 ms): (a) Grand-average waveforms of the ERPs recorded to the standard Gabors (including only non-target Gabor patches) when testing the amblyopic eye (red dashed line) and the fellow eye (red solid line) in amblyopes, and the left (black dashed line) and right eye (black solid line) in neurotypical observers. (b) Topographical scalp maps of the ERP activity. Waveforms and scalp maps show lower amplitude of the P2 component in the amblyopic eye

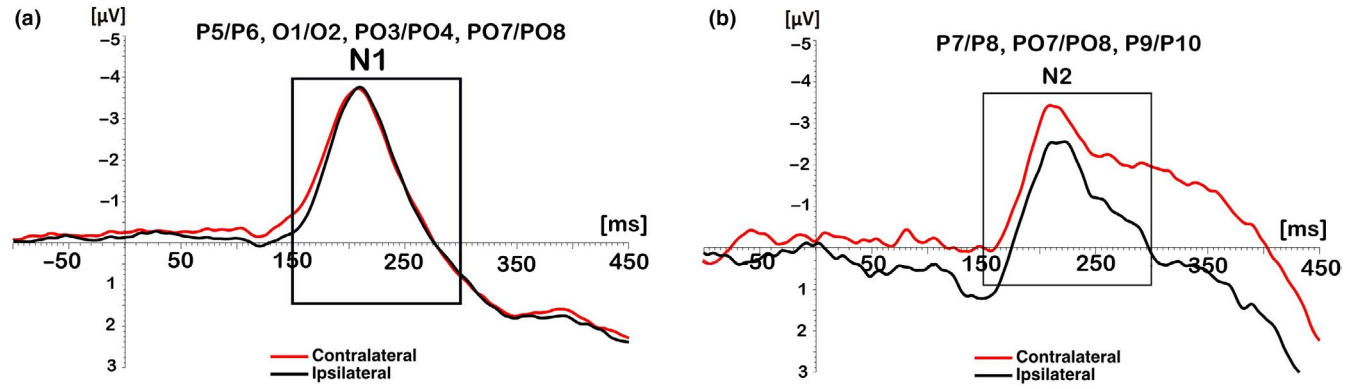

FIGURE 6 (a) ERPs recorded contralateral to the cued Gabor patches (standard trials, red line) and ipsilateral to the cued Gabor patches (black line). (b) ERPs recorded to validly cued Gabor patch targets over contralateral electrode sites (target trials, red line) and ipsilateral electrode sites (black line)

peak latency difference in the amblyopic observers. The main effect of Laterality revealed shorter latencies for ERPs that were recorded at sites contralateral to the cued location of the visual field ($F(1,12) = 4.926$, $p = .046$, $\eta_p^2 = 0.291$; contralateral: mean = 208.174 ms; $SE = 3.964$) compared to the ipsilateral sites (ipsilateral: mean = 212.508; $SE = 4.054$).

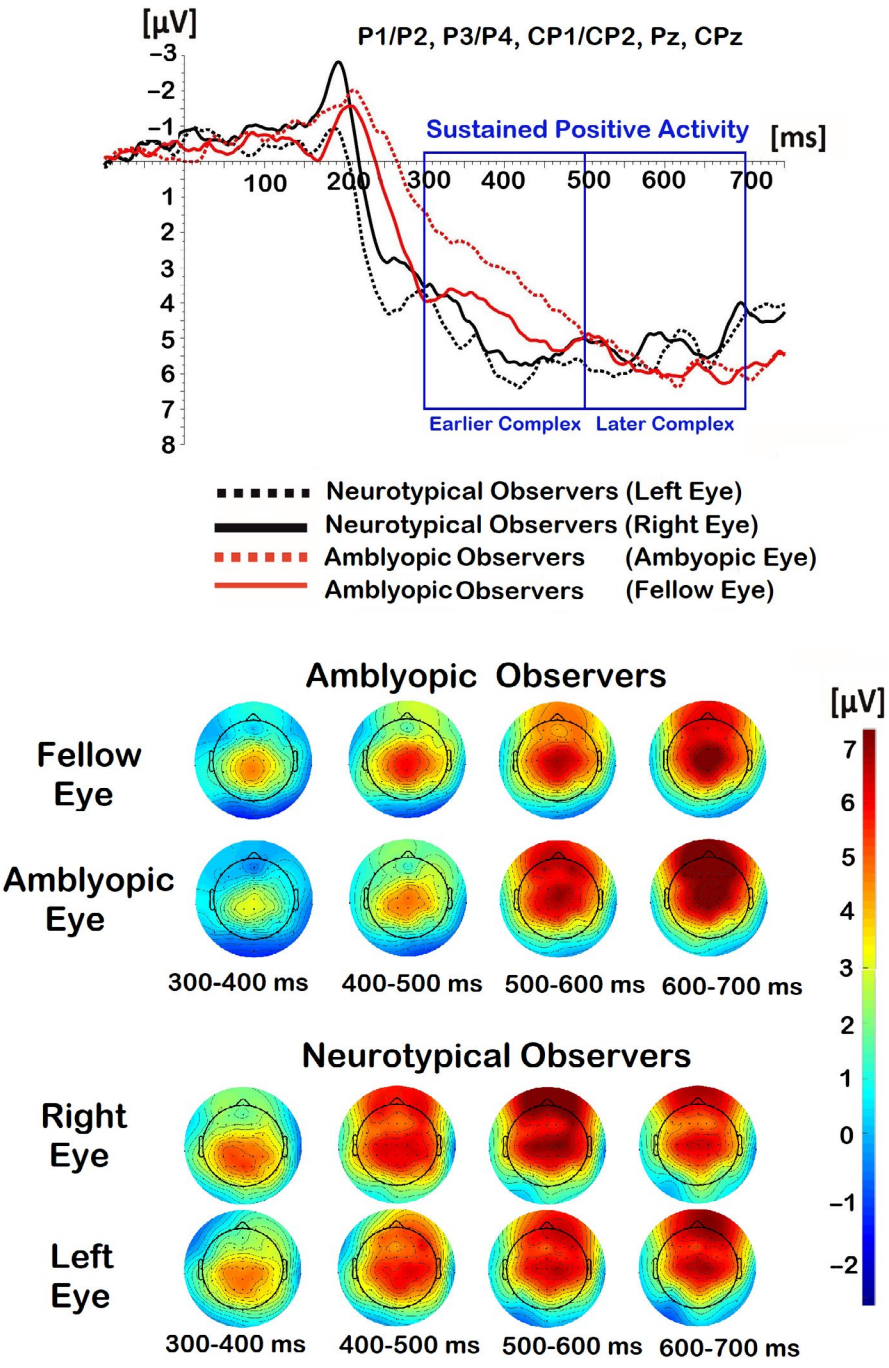

FIGURE 7 Earlier (300–500 ms) and later (500–700 ms) complexes of the late sustained positive ERP activity. (a) Grand-average waveforms of the ERPs recorded to the standard Gabors (including only non-target Gabor patches) when testing the amblyopic eye (red dashed line) and the fellow eye (red solid line) in amblyopes, and the left (black dashed line) and right eye (black solid line) in neurotypical observers. (b) Topographical scalp maps of the ERP activity. Waveforms and scalp maps show lower amplitude of the late sustained ERP activity in the 300-500 ms time-window for the amblyopic eye

The ANOVA did not reveal any other significant main or interaction effects (see Figure 6a, see Figure 8d).

4.2.4 | Correlation between posterior N1 peak latency (Ipsilateral minus Contralateral) and contrast values of the Gabor patches when testing the amblyopic eye

We correlated the ERP latency shifts in the time range of the visual posterior N1 (ERP peak latency recorded at ipsilateral electrode sites minus ERP peak latency recorded at contralateral electrode sites, both time-locked to the standard non-target Gabor patch) for the amblyopic eye with the contrast values measured in each amblyopic observer. This correlation was not significant ($r(7) = -.267$, $p = .562$).

4.2.5 | P2 (150–350 ms)

The P2 component was studied using the most positive local peak in the time-window of 150–350 ms post-onset of the standard Gabor patches. The latency of this peak was considered the peak latency of the P2 component. The findings are

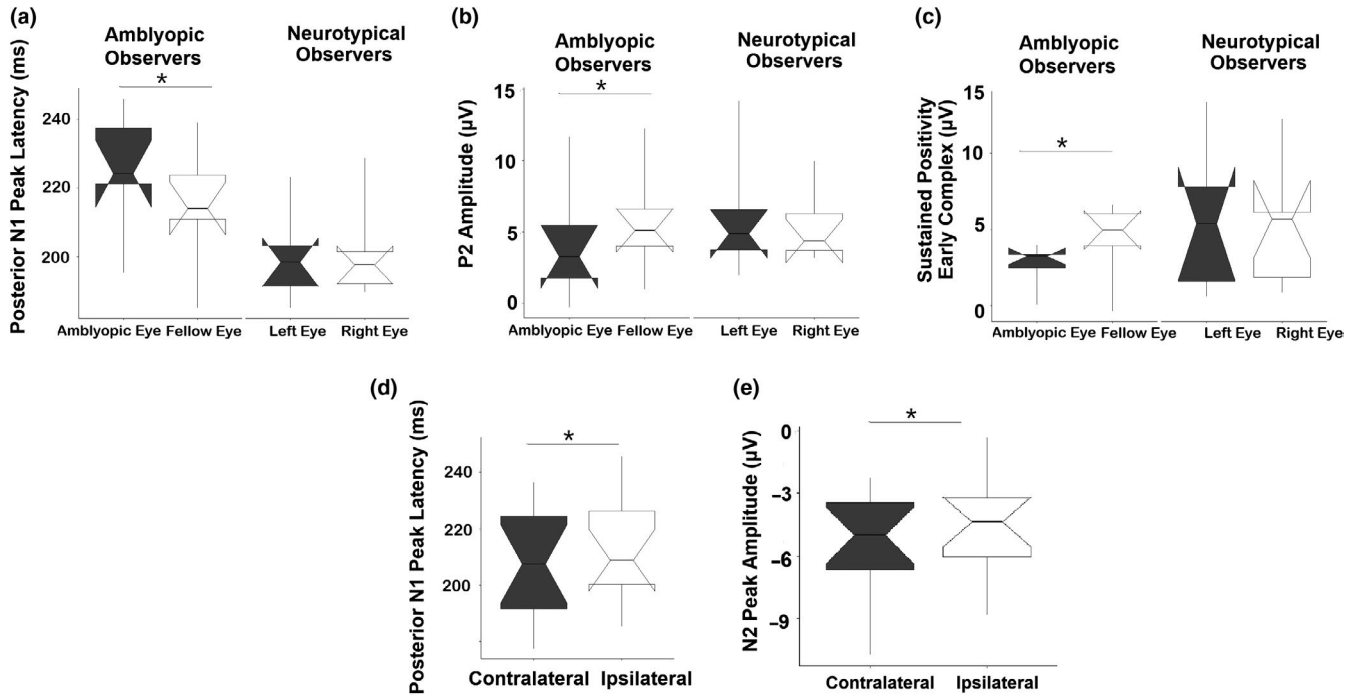

FIGURE 8 Box-whisker plots showing (a) Posterior N1 Peak Latency (ms), (b) P2 Amplitude (μV), (c) Sustained Positivity Early Complex (μV), (d) Posterior N1 Peak Latency (ms), (e) N2 Peak Amplitude. Box and whiskers show the spread of the measures (minimum, first and third interquartile ranges, and maximum). The notch in the boxplots indicates 95% confidence intervals. Stars indicate$p < .05$

presented for a central-anterior cluster including electrode pairs Fz, FCz, Cz, F1/F2, FC1/FC2 and C1/C2 (Table 3).

4.2.6 | P2: Peak amplitude

The ANOVA analyses on peak amplitudes of P2 component revealed a significant *Eye* by *Group* interaction ($F(1,12) = 6.094$, $p = .030$, $\eta_p^2 = 0.337$). Follow-up post hoc analyses revealed that the peak amplitude of the P2 component is significantly lower in the amblyopic eye (mean = 4.148 μV, $SE = 1.540$) compared to the fellow eye in individuals with amblyopia (mean = 5.640 μV, $SE = 1.156$; $t(6) = -3.830$, $p = .009$). No such interocular difference was observed between the right and left eyes of the neurotypical observers (left eye: mean = 5.978 μV, SE = 1.540; right eye: mean = 5.358 μV, SE = 1.156; $t(6) = 0.814$, $p = .447$). No other main or interaction effects were statistically significant ($p_s > .1$, see Table 2, see Figure 5, right side).

4.2.7 | P2: Peak latency

For the peak latency of the P2 component, none of the main or interaction effects of the ANOVA analyses were statistically significant (p-values >0.1), rendering the groups, eyes, and activity sides comparable to each other.

4.2.8 | Sustained positive activity (300–700 ms)

As described in Section 2.5, a longer epoch was created to capture the long latency ERP activity. This sustained positive activity was divided into an earlier complex between 300–500 ms and a later complex in the time-window 500–700 ms. The mean amplitude in these time ranges were calculated for each of these time periods and submitted to the ANOVA analyses. The findings are presented for a central-posterior cluster including electrode sites Pz, CPz, CP1/CP2, P1/P2 and P3/P4.

The ANOVA analyses on the mean amplitude of the earlier sustained positivity complex (300–500 ms) revealed a significant *Eye* by *Group* interaction effect ($F(1, 12) = 11.6$, $p = .005$, $\eta_p^2 = 0.49$). Follow-up t-tests indicated that the fellow eye (mean = 4.45 μV, $SE = 1.28$) of the amblyopic observers had higher mean amplitudes when compared to the amblyopic eye (mean = 2.67 μV, $SE = 1.23$; $t(6) = -3.55$, $p = .012$). No such interocular difference was found between the right (mean = 4.97 μV, $SE = 1.23$) and left (mean = 5.45 μV, $SE = 1.28$) eyes of the neurotypical observers ($t(6) = 1.11$, $p = .31$). No other main or interaction effects was statistically significant ($p_s > .1$), making the groups, eyes and sides comparable in this earlier time-window of the late sustained positive activity.

The ANOVA analyses on the mean amplitude of the later complex (500–700 ms) of this positive sustained activity showed no statistically significant main or interaction effects

TABLE 3 Visual ERPs

	Posterior N1 (150–300 ms) Latency			Posterior N1 (150–300 ms) Peak amplitude		
	F	*p*	η_p^2	*F*	*p*	η_p^2
Group	7.136	.020	0.374	0.893	.363	0.069
Eye	5.585	.036	0.318	3.166	.101	0.209
Eye*Group	8.144	.015	0.404	1.386	.262	0.104
Laterality	4.926	.046	0.291	0.441	.519	0.035
Laterality*Group	0.648	.436	0.051	1.065	.322	0.082
Eye*Laterality	0.607	.451	0.048	0.081	.781	0.007
Laterality*Eye*Group	2.578	.134	0.177	0.018	.896	0.001
	P2 (150–350 ms) Latency			**P2 (150–350 ms) Peak amplitude**		
	F	*p*	η_p^2	F	*p*	η_p^2
Group	0.263	.617	0.021	0.170	.687	0.014
Eye	0.004	.949	0.000	1.039	.328	0.080
Eye*Group	0.003	.956	0.000	6.094	.030	0.337
Laterality	0.618	.447	0.049	0.252	.625	0.021
Laterality*Group	2.332	.153	0.163	0.468	.507	0.038
Eye*Laterality	0.203	.660	0.017	0.144	.711	0.012
Laterality*Eye*Group	0.371	.554	0.030	0.964	.346	0.074
Sustained positive ERP activity (300−700ms)	**Mean amplitude Earlier complex (300−500ms)**			**Mean amplitude Later complex (500−700ms)**		
	F	*p*	η_p^2	*F*	*p*	η_p^2
Group	0.880	.367	0.068	0.037	.850	0.003
Eye	3.752	.077	0.238	0.208	.656	0.017
Eye*Group	11.599	.005	0.492	0.772	.397	0.060
Laterality	0.903	.361	0.070	0.022	.884	0.002
Laterality*Group	2.949	.112	0.197	0.508	.490	0.041
Eye*Laterality	2.271	.158	0.159	0.179	.679	0.015
Laterality*Eye*Group	0.818	.383	0.064	0.666	.430	0.053

(*p*s> 0.1). Thus, the interocular difference found in the earlier complex of this late sustained activity is not present at a later time period (see Figures 7 and 8c).

4.2.9 | ERPs to targets: N2 (150–300 ms)

Despite the low number of target trials, we investigated the laterality effect (contralateral vs. ipsilateral) to validly cued target Gabor patches in response to target trials. The ANOVA including the factors *Laterality* (contra vs. ipsilateral), *Eye* (left eye/right eye in neurotypical observers and amblyopic eye vs. fellow eye in amblyopic observers) and the between subject factor *Group* (amblyopic observers vs. neurotypical observers) on the peak amplitude of the N2 component, revealed a main effect of *Laterality* ($F(1,12) = 7.5$, $p = .018$, $\eta_p^2 = 0.061$) indicating higher peak amplitudes for ERPs recorded over contralateral electrodes to the cued Gabor patch target versus ipsilateral to the cued Gabor patch target (mean contralateral: −5.6 μV, SE: 0.93; mean ipsilateral: −4.7 μV, SE: 0.74). All other main or interaction effects were not significant, all ps> 0.150 (see Figure 6b, see Figure 8 E).

5 | DISCUSSION

The goal of the present ERP study was to understand the neural mechanisms of endogenous audio-visual spatial selective attention in human amblyopia and to link those findings to behavioural performance. Therefore, we applied a spatial cueing paradigm in which an auditory cue indicated the most likely location of an upcoming target Gabor patch which was presented together with another non-target Gabor Patch in the lower visual field. Participants were asked to detect the target Gabor patch, if any, at the validly cued location as fast and as correctly as possible. ERPs were recorded to the onset of the more frequently presented standard non-target Gabor patches, which did not require any motor responses.

Our findings indicate significantly higher rates of responses and reduced misses for locations that were validly cued with an auditory cue compared to the invalidly cued locations. The very low response rate for the invalidly cued trials suggests that participants were able to follow task instructions and distinguish task-relevant from task-irrelevant information similarly as reported in other cueing tasks (e.g., Eimer, 1994; Sylvester et al., 2007). This was observed in the entire sample regardless of the eye tested. That is in line with Sharma et al., (2000), Roberts et al., (2016) and Ramesh et al., (2020), who reported more accurate responses to target Gabor patches on the validly cued side and suggest that both amblyopic observers and neurotypical observers profit from the auditory cue. Interestingly, neural correlates support those findings: ERPs to validly cued standard Gabor patches occurred earlier over contralateral compared to ipsilateral scalp sites in all participants. Furthermore, the ERPs recorded to visual targets in the time range of the N2 showed a more pronounced negativity to contralateral compared to ipsilateral electrode sites across all participants. Thus, the ability to categorize a stimulus as a target as well as to attend to a precued spatial locations does not seem to differ in amblyopic compared to neurotypical observers (Luck, 2014). The attentional modulations found in the peak latency of the posterior N1, which was also observed in the amblyopic observers and their affected eye, does not seem to be related to stimulus contrast levels used in the experiment for these participants. This was established by a lack of significant correlation between the degree of attentional modulation in latency of the posterior N1 component and the individual contrast levels.

Furthermore, amblyopic observers in this study were not found to have a less accurate behavioural performance when contrasted to the neurotypical observers as shown by the comparable D-prime. Comparable D-prime in the amblyopic eye and the fellow eye also suggests that the contrast adaptation procedure applied to both eyes of the amblyopic observers before running the experimental paradigm were successful in equating performance with of the two eyes. The similar slopes of the regression lines between D-prime and RTs to validly cued Gabor patches for the amblyopic and fellow eyes is another confirmation of this assumption (see Figure 4). As for speed, individuals with amblyopia showed no difference when using the amblyopic or the fellow eye, as shown by the comparable RTs between the two eyes. However, combining accuracy measures with the speed dynamics of behaviour to look at the speed-accuracy-trade-off in our sample revealed an interocular difference in the amblyopic observers. Significantly higher IE scores (i.e., lower efficiency) were observed when testing the amblyopic eye compared to the fellow eye in amblyopic individuals only, suggesting that performing the task with the amblyopic eye leads to less efficient behaviour than performing the task with the fellow eye. This is consistent with other experimental tasks focusing on RTs as a dependent measurement and reporting worse performance when testing the amblyopic eye compared to the fellow eye (Bedell et al., 1990; Ho et al., 2006; Schor & Levi, 1980a, 1980b; Sharma et al., 2000).

The less efficient behavioural performance of the amblyopic eye was also reflected in the underlying neural activity on multiple levels. A significantly delayed neural response was observed in the amblyopic eye compared to the fellow eye only 200 ms after exposure to standard non-target Gabor patches. This delayed peak activity in the time-range of posterior N1 component was also observed when comparing all amblyopic observers (irrespective of the eyes being tested) with the neurotypical observers. The posterior N1 is assumed to be generated in the lateral occipital cortex and seems to be related to early visual attention processes (stimulus discrimination and detection) (Luck, 2005, p. 37). There are also studies showing a connection between the posterior N1 and elements of spatial attention (Hillyard et al., 1998; Mangun, 1995). Therefore, a further conclusion from our findings of a delayed posterior N1 peak could be drawn towards delayed neuronal processing mechanisms and even delayed early visual spatial attention processes for individuals with amblyopia compared to neurotypical observers and also for the amblyopic eye itself, when compared to the fellow eye. This is in line with previous reports indicating delayed latencies and reduced amplitudes of visual ERPs or SSVEPs in the amblyopic individuals (Arden et al., 1974; Banko et al., 2014; Hou et al., 2016; Kubová et al., 1996; Manny & Levi, 1982; McKerral et al., 1999; Sokol, 1983). Additionally, research on strabismic cats has shown an increase in latency of neural responses as well as an increase in internal noise when stimulating the amblyopic eye compared to the fellow eye (Singer et al., 1980). In an effort to link the neural and behavioural findings, it could be suggested that the delayed neural processes contributed significantly to the less efficient behaviour of the amblyopic eye.

Further inspection of the temporal visual processing hierarchy reveals that the P2 ERP component was less positive in the amblyopic eye compared to the fellow eye. It has

been suggested that the visual P2 component is involved in cognitive processes (such as perceptual grouping, Schendan & Lucia, 2010; and memory processes; Dunn et al., 1998) and is generated in parieto-occipital regions (Freunberger et al., 2007). ERPs of the amblyopic eye are slightly delayed and significantly reduced in amplitude in the time range of P2 which might point to higher cognitive deficiencies besides early perceptual deficits. In fact, a similar result can be seen for the positive ERP amplitudes that appear later in time and have a sustained nature. A weaker sustained positive activity in the time-range of 300–500 ms was found for the amblyopic eye compared to the fellow eye, paralleling the attenuated P2 activity in the amblyopic eye. Several previous studies have shown that in addition to impaired low level processing, amblyopia also involves higher order processing deficits which relate to object processing, global shape detection (Hess et al., 1999), real world scene processing (Mirabella et al., 2011), motion processing (Simmers et al., 2003) and feature counting (Sharma et al., 2000). Some authors argue that impaired object processing might be due to "sparse sampling" at the level of early visual cortex (Banko et al., 2013; Levi & Klein, 1986). To summarize, evidence of delayed and lower neural responses to visual stimuli in a visual-spatial attention task, which appears not to be limited to earlier stages of processing, are consistent with the suggestion that the neural resources allocated to the early formation of visual discriminative processes as well as later stimulus recognition and memory updating procedures are altered in the amblyopic eye.

The neural mechanisms when testing the amblyopic eye versus the fellow eye have been previously explored in human amblyopia at different regions along the central visual pathways. The findings point to an attenuated neuronal activity in the thalamus (Hess et al., 2009), decreased axonal density and myelination in the thalamo-cortical pathways (Allen et al., 2015), structural changes and a reduced activity of the lateral geniculate nucleus (Barnes et al., 2010; Hess et al., 2009). Moreover, abnormalities in the cortical visual area V1, such as a reduced neural activation, a reduced number of binocular cells and reduced number of cells driven by the amblyopic eye have been reported (Barnes et al., 2001; Goodyear et al., 2000; Kiorpes, 2006; Kiorpes & McKee, 1999; Levi, 2013). Impairments in areas beyond primary visual cortex have also been observed, such as a reduced blood flow in extrastriate visual areas (e.g. in Brodmann Area 18, 19; Imamura et al., 1997), reduced activation in V2 and in visual area V3A (Barnes et al., 2001; Bonhomme et al., 2006; Conner et al., 2007; Lerner et al., 2006; Li et al., 2007; Muckli et al., 2006) and impaired activation in area MT in which fewer cells responded to stimulation of the amblyopic eye after the presentation of moving stimuli (Ho & Giaschi, 2009; Secen et al., 2011). Moreover, a reduction of responses to stimulation of the amblyopic eye by presenting visual gratings was observed in V4+/V8 and LO complex as compared to V1/V2 in both anisometropic and strabismic amblyopic observers (Muckli et al., 2006), suggesting an impaired feedforward mechanism from primary visual areas to higher visual areas. Interestingly, higher level attention related areas, such as the frontal eye field, and the parietal cortex (two main areas of the attentional network) have also been shown to be less recruited when patients were asked to track multiple moving objects with their amblyopic eye compared to their fellow eye (Secen et al., 2011). The authors suggested that especially under high load conditions, impairments in the attentional network recruitment were observed in individuals with amblyopia. The results reported above, document a high range of activation patterns including lower and higher areas of the visual-spatial attentional network in amblyopia individuals (abnormalities in the visual cortical area V1: e.g., Barnes et al., 2001; Goodyear et al., 2000; Kiorpes, 2006; Kiorpes & McKee, 1999; Levi, 2013, 2020; Secen et al., 2011). This could be attributed to different kinds of stimulus material (gratings, faces, buildings and moving stimuli) used in these studies that involve activation of different brain regions (e.g. higher cortical areas are involved when the complexity of the stimulus material increased) and enhanced attentional control when task load increased such as in the MOT task: checkerboards have been included to tag brain responses in V1 and LGN (Miki et al., 2003); faces, and houses were presented to investigate extrastriate visual areas such as the fusiform gyrus (Lerner et al., 2006); moving stimuli were involved to investigate area MT but also the fronto-parietal cortical networks: (Secen et al., 2011; see also Joly & Franko, 2014 for a review). Moreover, different imaging methods and a variety in participant samples might be further sources of the heterogeneous results. A two-step process model was proposed by Muckli et al. (2006) who suggested a prenatal disposition leading to an impairment of the brain mechanisms responsible for binocular fusion which in turn leads to a "disuse of the central pathway" (p. 523). Muckli et al. (2006) observed that stimulating the amblyopic eye leads to lower activations in increasingly higher cortical levels in individuals with amblyopia. The authors suggest that the activity from the amblyopic eye is impaired when it is passed to higher areas. However, it is difficult to discern whether the reduced activity pattern of the amblyopic eye is related to impaired feed-forward (bottom-up) processes and/or feed-back related (top-down) processes.

In sum, evidence from past research suggests an altered involvement of lower as well as higher functional areas in the visual-spatial attentional network. The findings of the present study support this notion by showing traces of delayed and attenuated neural responses at early and late temporal stages of processing with each having their neural generators at lower

(posterior N1) or higher (P2 and sustained positive activity) areas of visual-spatial attention network.

One limitation of our study was requiring participants to execute a response only to the targets at cued spatial locations. Thus, the higher response rate of amblyopic observers in response to target stimuli at validly cued locations as compared to invalidly cued locations in our study cannot be exclusively attributed to preserved top-down attentional processes. Future studies using paradigms with similar task requirements for cued and uncued target stimuli can relate our findings more strongly to an intact top-down attentional capacity, as performed previously by Roberts et al. (2016). The inclusion of validly and invalidly cued target trials could also further reveal whether the delayed neural processes characterize affected attentional modulation or slowed visual processing. Furthermore, the low number of target trials in our design, which resulted in low signal to noise ratio for ERPs following target stimuli or motor-responses, did not allow the investigation of more memory- and executive-function related ERP components, beside P2 and late sustained activity, such as the P3b and lateralized-readiness potential (LRP). Nevertheless, a lengthy study design might result in fatigue and lead to artefacts or undesired neural responses. Thus, future studies with focus on such ERP components could shed more light on the more complex and higher functional stages of visual-spatial attention.

We did not apply any adjustments for multiple comparisons thus increasing the chance of false positive findings. However, we do not believe that this has an effect on the results and interpretation of the current findings due to the following reasons:

Firstly, the ERP components investigated in this study, such as N1 and P2, are very well-characterized by past research (Luck, 2014) and are found to be underlined by the visual and attention-related processes we investigated in our paradigm.

Secondly, we applied objective methods of identifying and quantifying ERP components using collapsed-localized waveforms and topography maps (Luck & Gaspelin, 2017).

Thirdly, we replicated our findings across different components, for instance the Eye by Group interaction showing lower/later peak/mean amplitude in the amblyopic eye compared to the fellow eye of the patients. This result pattern was observed in three different ERP components: N1, P2, and the late sustained positive activity. Moreover, the higher/earlier peak amplitudes for the contralateral versus ipsilateral activity, attributed to preferential neural processing related to the attended location was found in two different components, namely the N1 and N2 component, which were each elicited by a different type of stimulus (N1 for the standard Gabor patches and N2 for the target Gabor patches).

Finally, the delay and attenuation of the ERP components observed in our study in patients with amblyopia are also reported by past research (see also Arden et al., 1974; Hou et al., 2016; Kubova et al., 1996; McKerral et al., 1999; Sokol, 1983; Van Balen & Henkes, 1962), allowing us to formulate a priori hypothesis about the neural activities being investigated.

5.1 | Conclusions

The present results show that event-related potentials during different temporal visual processing stages are delayed or reduced in amplitude when testing the amblyopic eye compared to the fellow eye in a visual spatial selective attention task. This suggests that neural mechanisms at different processing hierarchies starting from perceptual to higher cognitive functions are restricted in the affected eye as a result of human amblyopia.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

D.L., M.N., C.G. and J.F. have designed the experiment, M.N. and C.G. have run the experiment, M.M., K.A. and J.E.A. have analysed the data, D.L., M.N., C.G., J.F. and M.M. have written the paper.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data used in this study are available on request to the corresponding author.

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